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Appendix F.7

Toxicity Profiles

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F.7.1 Antimony

F.7.1.1 Pharmacokinetics

Ingested antimony is absorbed slowly and incompletely from the gastrointestinal (GI) tract (Iffland 1988). Within a few days of acute exposure, highest tissue concentrations are found in the liver, kidney, and thyroid. Organs of storage include skin, bone, and teeth. Highest concentrations in deceased smelter workers (inhalation exposure) occurred in the lungs and skeleton. Excretion is largely via the urine or feces, although some is incorporated into the hair.

F.7.1.2 Noncancer Toxicity

Acute intoxication from ingestion of large doses of antimony induces GI disturbances, dehydration, and cardiac effects in humans (Iffland 1988). Chronic effects from occupational exposure include irritation of the respiratory tract, pneumoconiosis, pustular eruptions of the skin called "antimony spots," allergic contact dermatitis, and cardiac effects, including abnormalities of the electrocardiograph (ECG) and myocardial changes. Cardiac effects were also observed in rats and rabbits exposed by inhalation for six weeks and in animals (dogs, and possibly other species) treated by intravenous injection (Elinder and Friberg 1986).

Chronic oral exposure studies in laboratory animals include two briefly reported lifetime drinking water studies in rats and mice (Kanisawa and Schroeder 1969; Schroeder et al. 1970). The only dose tested, 5 ppm potassium antimony tartrate, resulted in reduced longevity in both species and in reduced mean heart weight in the rats. The EPA (2000) verifies a RfD of 0.0004 mg/kg/day for chronic oral exposure to antimony from the LOAEL of 5 ppm potassium antimony tartrate (0.35 mg antimony/kg body weight-day) in the lifetime study in rats (Schroeder et al. 1970). An uncertainty factor of 1000 was applied; factors of 10 each for inter- and intraspecies variation and to estimate an NOAEL from an LOAEL. The heart is considered a likely target organ for chronic oral exposure of humans.

F.7.1.3 Carcinogenicity

Data were not located regarding the carcinogenicity of antimony to humans. Antimony fed to rats did not produce an excess of tumors (Goyer 1991), but a high frequency of lung tumors was observed in rats exposed by inhalation to antimony trioxide for one year (Elinder and Friberg 1986). Antimony is classified in EPA cancer weight-of-evidence Group D (not classifiable as to carcinogenicity to humans) (EPA 1997).

F.7.2 Arsenic

F.7.2.1 Pharmacokinetics

Several studies confirm that soluble inorganic arsenic compounds and organic arsenic compounds are almost completely (>90 percent) absorbed from the GI tract in both animals and humans (Ishinishi et al. 1986). The absorption efficiency of insoluble inorganic arsenic compounds depends on particle size and stomach pH. Initial distribution of absorbed arsenic is to the liver, kidneys, and lungs, flowed by redistribution to hair, nails, teeth, bone, and skin, which are considered tissues of accumulation. Arsenic has a long half-life in the blood of rats, compared with other animals and humans, because of firm binding to the hemoglobin in erythrocytes.

Metabolism of inorganic arsenic includes reversible oxidation-reduction so that both arsenite (valence of 3) and arsenate (valence of 5) are present in the urine of animals treated with arsenic of either valence (Ishinishi et al. 1986). Arsenite is subsequently oxidized and methylated by a saturable mechanism to form mono- or dimethylarsenate; the latter is the predominant metabolite in the urine of animals or humans. Organic arsenic compounds (arsenilic acid, cacodylic acid) are not readily converted to inorganic arsenic. Excretion of organic or inorganic arsenic is largely via the urine, but considerable species variation exists. Continuously exposed humans appear to excrete 60 to 70 percent of their daily intake of arsenate or arsenite via the urine.

F.7.2.2 Noncancer Toxicity

A lethal dose of arsenic trioxide in humans is 70 to 180 mg. (approximately 50 to 140 mg arsenic; Ishinishi et al. 1986). Acute oral exposure of humans to high doses of arsenic produces liver swelling, skin lesions, disturbed heart function, and neurological effects. The only noncancer effects in humans clearly attributable to chronic oral exposure to arsenic are dermal hyperpigmentation and keratosis, as revealed by studies of several hundred Chinese exposed to naturally occurring arsenic in well water (Tseng 1977; Tseng et al. 1968; EPA 2000). Similar effects were observed in persons exposed to high levels of arsenic in water in Utah and the northern part of Mexico (Cebrian et al. 1983; Southwick et al. 1983). Occupational (predominantly inhalation) exposure is also associated with neurological deficits, anemia, and cardiovascular effects (Ishinishi et al. 1986), but concomitant exposure to other chemicals cannot be ruled out. The EPA (2000) derived a RfD of 0.3 ug/kg/day for chronic oral exposure, based on an NOAEL of 0.8 ug/kg/day for skin lesions from Chinese data. The principal target organ for arsenic appears to be the skin. The nervous system and cardiovascular systems appear to be less significant target organs. Inorganic arsenic may be an essential nutrient, exerting beneficial effects on growth, health, and feed conversion efficiency (Underwood 1977).

F.7.2.3 Carcinogenicity

Inorganic arsenic is clearly a carcinogen in humans. Inhalation exposure is associated with increased risk of lung cancer in persons employed as smelter workers, in arsenical pesticide applicators, and in a population residing near a pesticide manufacturing plant (EPA 2000). Oral exposure to high levels in well water is associated with increased risk of skin cancer (Tseng 1977; EPA 2000). Extensive animal testing with various forms of arsenic given by many routes of exposure to several species, however, has not demonstrated the carcinogenicity of arsenic (International Agency for Research on Cancer [IARC] 1980). The EPA (2000) classifies inorganic arsenic in cancer weight-of-evidence Group A (human carcinogen), and recommends an oral unit risk of 0.00005 ug/L in drinking water, based on the incidence of skin cancer in the Tseng (1977) study. The EPA presents a chronic oral slope factor of 1.5 per mg/kg/day based on the same information. The EPA (2000) notes that the uncertainties associated with the oral unit risk are considerably less than those for most

carcinogens, so that the unit risk might be reduced in order of magnitude. An inhalation unit risk of 0.0043 per ug/m^3 was derived for inorganic arsenic from the incidence of lung cancer in occupationally exposed men (EPA 2000). An inhalation cancer slope factor, equivalent to 15.1 per mg/kg/day, was derived from the same data assuming an inhalation rate of 20 m^3/day and a body weight of 70 kg for humans.

F.7.3 Barium

F.7.3.1 Noncancer Toxicity

Barium is a naturally occurring alkaline earth metal that comprises approximately 0.04 percent of the earth's crust (Reeves 1986). Acute oral toxicity was manifested by GI upset, altered cardiac performance, and transient hypertension, convulsions, and muscular paralysis. Repeated oral exposures were associated with hypertension. Occupational exposure to insoluble barium sulfate induced benign pneumoconiosis (ACGIH 1991). The EPA (2000) presents a verified chronic oral RfD of 0.07 mg/kg/day, based on an NOAEL of 0.21 mg/kg/day in a ten-week study in humans exposed to barium in drinking water and an uncertainty factor of 3. The EPA (1997) presented the same value as a provisional RfD for subchronic oral exposure. A provisional chronic inhalation RfC of 0.0005 mg/m^3 and a provisional subchronic inhalation RfC of 0.005 mg/m^3 were based on a NOEL for fetotoxicity in a four-month intermittent-exposure inhalation study in rats (EPA 1997). Uncertainty factors of 1000 and 100 were used for the chronic and subchronic RfC values, respectively. The chronic and subchronic inhalation RfC values are equivalent to 0.0001 and 0.001 mg/kg/day, assuming a human inhalation rate of 20 m^3/day and body weight of 70 kg. Barium is principally a muscle toxin. Its targets are the GI system, skeletal muscle, the cardiovascular system, and the fetus.

F.7.3.2 Carcinogenicity

The EPA (2000) classifies barium as a cancer weight-of-evidence Group D substance (not classifiable as to carcinogenicity in humans). Cancer risk is not estimated for Group D substances.

F.7.4 Cadmium

F.7.4.1 Pharmacokinetics

Estimates of cadmium uptake by the respiratory tract range from 10 to 50 percent; uptake is greatest for fumes and small particles and least for large dust particles (Friberg et al., 1986; Goyer, 1991). GI absorption of ingested cadmium is ordinarily 5 to 8 percent, but may reach 20 percent in cases of serious dietary ion deficiency. Highest tissue levels are normally found in the kidneys followed by the liver, although levels in the liver may exceed those in the kidneys of persons suffering from cadmium-induced renal dysfunction. The half-life of cadmium in the kidneys and liver may be as long as 10-30 years. Fecal and urinary excretion of cadmium are approximately equivalent to normal humans exposed to small amounts. Urinary excretion increases markedly in humans with cadmium-induced renal disease.

F.7.4.2 Noncancer Toxicity

Acute inhalation exposure to fumes or particles of cadmium induces respiratory symptoms, general weakness, and, in severe cases, respiratory insufficiency, shock, and death (Friberg et al., 1986). Acute oral exposure induces GI disturbances. Chronic inhalation exposure induces pulmonary emphysema, and chronic exposure by either route consistently produces renal tubular disease in humans and laboratory animals. Proteinuria is a reliable early indicator of cadmium-induced kidney disease. The combination of pulmonary emphysema and renal tubular disease, if severe, may result in early mortality. Painful osteomalacia and osteoporosis may arise from altered metabolism of bone minerals secondary to renal damage. The combination of renal and skeletal damage is called itai-itai disease in Japan. Cadmium exposure ahs been associated with liver damage, but the liver appears to be less sensitive than the kidney. The kidney is the primary target organ of cadmium toxicity. The EPA (2000) derived chronic oral RfD values of 0.5 ug/kg/day for cadmium ingested in water and 1 ug/kg/day for cadmium ingested in food, based on a toxicokinetic model that predicted NOAELs from renal cortical concentration of cadmium. The different RfD values reflect assumed differences in GI absorption of cadmium from water (5 percent) and food (2.5 percent).

F.7.4.3 Carcinogenicity

Carcinogenicity data in humans consist of several occupational studies that associate cadmium exposure with lung cancer, but concomitant exposure to other carcinogenic chemicals and smoking were not adequately controlled. Other occupational studies reported significantly increased risk of prostatic cancer, but this effect was not observed in the largest occupational study of workers exposed to high levels (Thun et al., 1985). The animal data consist of an inhalation study in rats that showed a significant increase in lung tumors, and several parenteral injection studies that produced injection site tumors. No evidence of carcinogenicity, however, was observed in seven oral studies in rats and mice. The EPA (2000) classifies cadmium a cancer weight-of-evidence Group B1 substance for inhalation exposure on the basis of limited evidence of carcinogenicity in humans and sufficient evidence in animals. The data were insufficient to classify cadmium as carcinogenic to humans exposed by the oral route. An inhalation unit risk of 0.0018 ug/m^3, equivalent to 6.3 per mg/kg/day, was derived from the occupational exposure study by Thun et al. (1985) assuming an inhalation rate of 20 m^3/day and a body weight of 70 kg for humans.

F.7.5 Chromium

F.7.5.1 Noncancer Toxicity

In nature, chromium (III) predominates over chromium (VI) (Langård and Norseth, 1986). Little chromium (VI) exists in biological materials, except shortly after exposure, because reduction to chromium (III) occurs rapidly. Chromium (III) is considered a nutritionally essential trace element and is considerably less toxic than chromium (VI). No effects were observed in rats consuming 5% chromium (III)/kg/day in the diet for over two years (EPA, 1997). The NOEL of 5% Cr2O3 was the basis for a verified chronic oral RfD of 1.5 mg/kg/day (EPA, 1997). The same NOEL and an uncertainty factor of 1000 were the basis for a provisional subchronic oral RfD of 1 mg/kg/day (EPA, 1997).

Acute oral exposure of humans to high doses of chromium (VI) induced neurological effects, GI hemorrhage and fluid loss, and kidney and liver effects. Parenteral dosing of animals with chromium (VI) is selectively toxic to the kidney tubules. An NOAEL of 2.4 mg chromium (VI)

/kg/day in a one-year drinking water study in rats and an uncertainty factor of 500 was the basis of a verified RfD of 0.003 mg/kg/day for chronic oral exposure (EPA, 2000). The same NOAEL and an uncertainty factor of 100 were the basis of a provisional subchronic oral RfD of 0.02 mg/kg/day (EPA, 1997).

Occupational (inhalation and dermal) exposure to chromium (III) compounds induced dermatitis (ACGIH, 1991). Similar exposure to chromium (VI) induced ulcerative and allergic contact dermatitis, irritation of the upper respiratory tract including ulceration of the mucosa and perforation of the nasal septum, and possibly kidney effects. An inhalation RfC values was not located for chromium (III), however, EPA (2000) presents an inhalation RfD of 0.03 ug/kg/day for chromium (VI).

A target organ was not identified for chromium (III). The kidney appears to be the principal target organ for repeated oral dosing with chromium (VI). Additional target organs for dermal and inhalation exposure include the skin and respiratory tract.

F.7.5.2 Carcinogenicity

Data were not located regarding the carcinogenicity of chromium (III). The EPA (2000) classifies chromium (VI) in cancer weight-of-evidence Group A (human carcinogen), based on the consistent observation of increased risk of lung cancer in occupational studies of workers in chromate production or the chrome pigment industry. Parenteral dosing of animals with chromium (VI) compounds consistently induced injection-site tumors. There is no evidence that oral exposure to chromium (VI) induces cancer. An inhalation unit risk of 0.012 per ug/m^3, equivalent to 41 per mg/kg/day, assuming humans inhale 20 m^3/day and weigh 70 kg, was based on increased risk of lung cancer deaths in chromate production workers (EPA, 2000).

F.7.6 Copper

F.7.6.1 Noncancer Toxicity

Copper is a nutritionally essential element that functions as a cofactor in several enzyme systems (Aaseth and Norseth 1986). Acute exposure to large oral doses of copper salts was

associated with GI disturbances, hemolysis, and liver and kidney lesions. Chronic oral toxicity in humans has not been reported. Chronic oral exposure of animals was associated with an iron-deficiency type of anemia, hemolysis, and lesions in the liver and kidneys. Occupational exposure may induce metal fume fever, and, in cases of chronic exposure to high levels, hemolysis and anemia (ACGIH 1991). Neither oral nor inhalation RfD or RfC values were located for copper. The target organs for copper are the erythrocyte, liver, and kidney, and, for inhalation exposure, the lung. An oral RfD of 0.04 mg/kg/day was presented for copper (EPA, 1997). A RfC value was not located for copper.

F.7.6.2 Carcinogenicity

Copper is classified in cancer weight-of-evidence Group D (not classifiable as to carcinogenicity to humans) (EPA 1997). Quantitative risk estimates are not derived for Group D chemicals.

F.7.7 Lead

F.7.7.1 Pharmacokinetics

Studies in humans indicate that an average of 10 percent of ingested lead is absorbed, but estimates as high as 40 percent were obtained in some individuals (Tsuchiya, 1986). Nutritional factors have a profound effect on GI absorption efficiency. Children absorb ingested lead more efficiently than adults; absorption efficiencies up to 53 percent were recorded for children three months to eight years of age. Similar results were obtained for laboratory animals; absorption efficiencies of 5 to 10 percent were obtained for adults and > 50 percent were obtained for young animals. The deposition rate of inhaled lead averages approximately 30 to 50 percent, depending on particle size, with as much as 60 percent deposition of very small particles (0.03 mm) near highways. All lead deposited in the lungs is eventually absorbed.

Approximately 95 percent of the lead in the blood is located in the erythrocytes (EPA, 2000). Lead in the plasma exchanges with several body compartments, including the internal organs, bone, and several excretory pathways. In humans, lead concentrations in bone increase with

age (Tsuchiya, 1986). About 90 percent of the body burden of lead is located in the skeleton. Neonatal blood concentrations are about 85 percent of maternal concentrations (EPA, 2000). Excretion of absorbed lead is principally through the urine, although GI secretion, biliary excretion, and loss through hair, nails, and sweat are also significant.

F.7.7.2 Noncancer Toxicity

The noncancer toxicity of lead to humans has been well characterized through decades of medical observation and scientific research (EPA, 2000). The principal effects of acute oral exposure are colic with diffuse paroxysmal abdominal pain (probably due to vagal irritation), anemia, and, in severe cases, acute encephalopathy, particularly in children (Tsuchiya, 1986). The primary effects of long-term exposure are neurological and hematological. Limited occupational data indicate that long-term exposure to lead may induce kidney damage. The principal target organs of lead toxicity are the erythrocyte and the nervous system. Some of the effects on the blood, particularly changes in levels of certain blood enzymes, and subtle neurobehavioral changes in children, appear to occur at levels so low as to be considered nonthreshold effects.

The USEPA (1986b and 1990a) determined that it is inappropriate to derive a RfD for oral exposure to lead for several reasons. First, the use of a RfD assumes that a threshold for toxicity exists, below which adverse effects are not expected to occur. However, the most sensitive effects of lead exposure, impaired neurobehavioral development in children and altered blood enzyme levels associated with anemia, may occur at blood lead concentrations so low as to be considered practically nonthreshold in nature. Second, RfD values are specific for the route of exposure for which they are derived. Lead, however, is ubiquitous, so that exposure occurs from virtually all media and by all pathways simultaneously, making it practically impossible to quantify the contribution to blood lead from any one route of exposure. Finally, the dose-response relationships common to many toxicants, and upon which derivation of a RfD is based, do not hold true for lead. This is because the fate of lead within the body depends, in part, on the amount and rate of previous exposures, the age of the recipient, and the rate of exposure. There is, however, a reasonably good correlation between blood lead concentration and effect. Therefore, blood lead concentration is the appropriate parameter on which to base the regulation of lead.

USEPA (1997) presented no inhalation RfC for lead, but referred to the National Ambient Air Quality Standard (NAAQS) for lead, which could be used in lieu of an inhalation RfC. The NAAQSs are based solely on human health considerations and are designed to protect the most sensitive subgroup of the human population. The NAAQS for lead is 1.5 mg/m^3, averaged quarterly.

F.7.7.3 Carcinogenicity

USEPA (2000) classifies lead in cancer weight-of-evidence Group B2 (probable human carcinogen), based on inadequate evidence of cancer in humans and sufficient animal evidence. The human data consist of several epidemiologic occupational studies that yielded confusing results. All of the studies lacked quantitative exposure data and failed to control for smoking and concomitant exposure to other possibly carcinogenic metals. Rat and mouse bioassays showed statistically significant increases in renal tumors following dietary and subcutaneous exposure to several soluble lead salts. Various lead compounds were observed to induce chromosomal alterations in vivo and in vitro, sister chromatic exchange in exposed workers, and cell transformation in Syrian hamster embryo cells; to enhance simian adenovirus induction; and to alter molecular processes that regulate gene expression. USEPA (1997) declined to estimate risk for oral exposure to lead because many factors (e.g., age, general health, nutritional status, existing body burden and duration of exposure) influence the bioavailability of ingested lead, introducing a great deal of uncertainty into any estimate of risk.

The USEPA IEUBK lead model is an iterated set of equations that estimate blood lead concentration in children aged 0 to 7 years (USEPA, 1994a). The biokinetic part of the model describes the movement of lead between the plasma and several body compartments and estimates the resultant blood lead concentration. The rate of the movement of lead between the plasma and each compartment is a function of the transition or residence time (i.e., the mean time for lead to leave the plasma and enter a given compartment, or the mean residence time for lead in that compartment). Compartments modeled include the erythrocytes, liver, kidneys, all the other soft tissue of the body, cortical bone, and trabecular bone. Excretory pathways and their rates are also modeled. These include the mean time for excretion from the plasma to the urine, from the liver to the bile, and from the other soft tissues to the hair, skin, sweat, etc. The model permits the user to adjust the transition and residence times.

USEPA guidance (USEPA, 1994b) recommends using 400 mg/kg as a screening level for lead in soil for residential scenarios at CERCLA sties and at RCRA Corrective Action sites. Residential areas with soil lead below 400 mg/kg generally require no further action. However, in some special situations, further study is warranted below the screening level (e.g., wetlands, agricultural areas).

F.7.8 Manganese

F.7.8.1 Noncancer Toxicity

Manganese is nutritionally required in humans for normal growth and health (EPA, 2000). Humans exposed to approximately 0.8 mg manganese/kg/day in drinking water exhibited lethargy, mental disturbances (1/16 committed suicide), and other neurologic effects. The elderly appeared to be more sensitive than children. Oral treatment of laboratory rodents induced biochemical changes in the brain, but rodents did not exhibit the neurological signs exhibited by humans. Occupational exposure to high concentrations in air induced a generally typical spectrum of neurological effects and an increased incidence of pneumonia (ACGIH, 1986).

EPA presented the oral RfD for manganese of 0.02 mg/kg/day (EPA, 2000) based on drinking water and an oral RfD of 0.14 mg/kg/day based on food. The EPA (2000) presented a verified chronic inhalation RfC based on a LOAEL for impairment of neurobehaviorial function in occupationally exposed humans. The inhalation RfC is equivalent to 0.0143 ug/kg/day, assuming humans inhale 20 m^3 of air/day and weigh 70 kg. The CNS and respiratory tract are target organs of inhalation exposure to manganese.

F.7.8.2 Carcinogenicity

The EPA (2000) classifies manganese in cancer weight-of-evidence Group D (not classifiable as to carcinogenicity to humans). Quantitative cancer risk estimates are not derived from Group D chemicals.

F.7.9 Mercury

Mercury occurs in three forms: elemental, organic, and inorganic. Although the toxicity of all forms is mediated by the mercury cation, the extent of absorption and pattern of distribution within the body, which determines the effects observed, depends on the form to which the organism is exposed (Goyer, 1991). Bacterial activity in the environment converts inorganic mercury to methyl mercury (Berlin, 1986). It is likely that either inorganic mercury or methyl mercury may be taken up by plants and enter the food chain, and this discussion will focus on inorganic and methyl mercury. Exposure to elemental mercury, which is more likely to occur in an occupational setting, is not discussed herein.

F.7.9.1 Pharmacokinetics

The GI absorption of inorganic mercury salts is about 2 to 10 percent in humans, and slightly higher in experimental animals (Berlin, 1986; Goyer, 1991). Inorganic mercury in the blood is roughly equally divided between the plasma and erythrocytes. Distribution is preferentially to the kidney, with somewhat lower concentrations found in the liver, and even lower levels found in the skin, spleen, testes, and brain (Berlin, 1986). Inorganic mercury is excreted principally through the feces and urine, with minor pathways including the secretions of exocrine glands and exhalation of elemental mercury vapor.

Methyl mercury is nearly completely (90 to 95 percent) absorbed from the GI tract (Berlin, 1986). The concentration of methyl mercury in the erythrocytes is about 10 times that in the plasma. Methyl mercury leaves the blood slowly, showing particular affinity for the brain, particularly in primates. In rats, 1 percent of the body burden of methyl mercury is found in the brain, but in humans, 10 percent of the body burden is found in the brain. Somewhat lower levels are found in the liver and kidney. During pregnancy, methyl mercury accumulates in the fetal brain, often at levels higher than in the maternal brain. Most tissues except the brain transform methyl mercury to inorganic mercury. Excretion of methyl mercury is principally via the bile, with a half-life of 70 days in humans not suffering from toxicity. Following exposure to methyl mercury, some of the mercury in the bile exists as methyl mercury and some as the inorganic form. The inorganic form is largely passed in the feces, but the methyl mercury is

subject to enterohepatic recirculation. Another important excretory pathway for methyl mercury is lactation.

F.7.9.2 Noncancer Toxicity

Target organs for inorganic or methyl mercury include the kidney, nervous system, fetus, and neonate. Acute oral exposure to high doses of inorganic mercury causes severe damage to the GI mucosa because of the corrosive nature of mercury salts, which may lead to bloody diarrhea, shock, circulatory collapse, and death (Berlin, 1986; Goyer, 1991). Acute sublethal poisoning induces severe kidney damage. Chronic exposure induces an autoimmune glomerular disease and renal tubular injury. The U.S. EPA (1997) presented a verified RfD of 0.3 ug/mg-day for chronic oral exposure to inorganic mercury, based on kidney effects in rats.

Acute or chronic exposure to methyl mercury leads to neurologic dysfunction (Berlin, 1986; Goyer, 1991). The region of the nervous system affected is species-dependent. Methyl mercury poisoning in rats induces peripheral nerve damage and kidney effects. In humans, the sensory cortex appears to be the most sensitive. The brain of the fetus and the neonate may be unusually sensitive to methyl mercury; retarded neurologic development was observed in prenatally exposed children whose mothers showed no clinical signs of poisoning. The U.S. EPA (1997) derived a RfD of 0.1 ug/kg/day for chronic oral exposure to methyl mercury based on developmental neurological abnormalities in human infants. An inhalation RfC of 0.0003 mg/m^3 (uncertainty factor of 30) has been established for inorganic mercury based on neurotoxic effects in humans. This translates into a chronic RfD of 0.000086 mg/kg/day (U.S. EPA, 2000).

F.7.9.3 Carcinogenicity

The U.S. EPA (2000) classifies inorganic mercury in cancer weight-of-evidence Group D (not classifiable as to carcinogenicity to humans), based on no data regarding cancer in humans, and inadequate animal and supporting data. In an intraperitoneal injection study with metallic mercury in rats, sarcomas developed only in those tissues in direct contact with the test material (ATSDR, 1992c). A two-year dietary study in rats with mercuric acetate (inorganic mercury) yielded no evidence of carcinogenicity (ATSDR, 1992c). In mice, however, dietary

exposure to high doses of mercury chloride for up to 78 weeks induced renal adenomas and adenocarcinomas (ATSDR, 1992c). The U.S. EPA has not yet evaluated the carcinogenicity of organic mercury. No carcinogenic effect, however, was observed in a two-year feeding study with phenylmercuric acetate in rats (ATSDR, 1992c).

F.7.10 Nickel

F.7.10.1 Noncancer Toxicity

In a subchronic gavage study with nickel chloride in water, clinical signs of toxicity in rats included lethargy, ataxia, irregular breathing, reduced body temperature, salivation, and discolored extremities (EPA 2000). Inhalation exposure was associated with asthma and pulmonary fibrosis in welders using nickel alloys (ACGIH 1986). Lung effects were observed in laboratory animals exposed by inhalation. The EPA (2000) presented a verified RfD of 0.02 for chronic oral exposure to nickel, based on an NOAEL for decreased organ and body weights in a two-year dietary study with nickel sulfate in rats and an uncertainty factor of 300. The EPA (1997) presented the same value as a provisional subchronic oral RfD. The CNS appears to be the target organ for the oral toxicity of nickel. The lung is clearly the target organ for inhalation exposure.

F.7.10.2 Carcinogenicity

Occupational exposure to nickel was associated with increased risk of nasal, laryngeal and lung cancer (ATSDR 1995). Inhalation exposure of rats to nickel subsulfide increased the incidence of lung tumors. The EPA (2000) presents a cancer weight-of-evidence Group A classification (human carcinogen) for nickel, and presents an inhalation unit risk of 0.00024 per mg/m^3 for nickel refinery dust. The unit risk is equivalent to 0.84 per ug/kg/day, assuming humans inhale 20 m^3 of air/day and weigh 70 kg. The quantitative estimate was derived from the human occupational studies.

F.7.11 Thallium

F.7.11.1 Noncancer Toxicity

Thallium is highly toxic; acute ingestion by humans or laboratory animals induced gastroenteritis, neurological dysfunction, and renal and liver damage (Kazantzis, 1986). Chronic ingestion of more moderate doses characteristically caused alopecia. Thallium was used medicinally to induce alopecia in cases of ringworm of the scalp, sometimes with disastrous results. In industrial (inhalation, oral, dermal) exposure, neurologic signs preceded alopecia, suggesting that the nervous system is more sensitive than the hair follicle. The EPA (2000) presented verified chronic oral RfD values for several thallium compounds (thallium acetate, thallium acetate, thallium carbonate, thallium chloride, thallium nitrate, thallium sulfate, and thallic oxide) based on increased incidence of alopecia and increased serum levels of liver enzymes indicative of hepatocellular damage in rats treated with thallium sulfate for 90 days. EPA (2000) presented a chronic oral RfD for thallium of 0.07 ug/kg/day.

F.7.11.2 Carcinogenicity

Thallium was classified as a cancer weight-of-evidence Group D substance (not classifiable as to carcinogenicity to humans) (EPA, 2000).

F.7.12 Vanadium

F.7.12.1 NONCANCER TOXICITY

The oral toxicity of vanadium compounds to humans is very low (Lagerkvist et al. 1986), probably because little vanadium is absorbed from the GI tract. Effects in humans exposed by inhalation include upper and lower respiratory tract irritation. A provisional subchronic and chronic oral RfD of 0.007 mg/kg/day was derived from an NOEL in rats in a lifetime drinking water study with vanadyl sulfate and an uncertainty factor of 100 (USEPA, 1997). A target organ could not be identified for oral exposure. The respiratory tract is the target organ for inhalation exposure.

F.7.12.2 Carcinogenicity

No information was located regarding the carcinogenicity of vanadium.

F.7.13 Zinc

F.7.13.1 Pharmacokinetics

Zinc is a nutritionally required trace element. Estimates of the efficiency of GI absorption of zinc in animals range from <10 to 90 percent (Elinder 1986). Estimates in normal humans range from approximately 20 to 77 percent (Elinder 1986; Goyer 1991). The net absorption of zinc appears to be homeostatically controlled, but it is unclear whether GI absorption, intestinal secretion, or both are regulated. Distribution of absorbed zinc is primarily to the liver (Goyer 1991), with subsequent redistribution to bone, muscle, and kidney (Elinder 1986). Highest tissue concentrations are found in the prostate. Excretion appears to be principally through the feces, in part from biliary secretion, but the relative importance of fecal and urinary excretion is species-dependent. The half-life of zinc absorbed from the GI tracts of humans in normal zinc homeostasis is approximately 162 to 500 days.

F.7.13.2 Noncancer Toxicity

Humans exposed to high concentrations of aerosols of zinc compounds may experience severe pulmonary damage and death (Elinder 1986). The usual occupational exposure is to freshly formed fumes of zinc, which can induce a reversible syndrome known as metal fume fever. Orally, zinc exhibits a low order of acute toxicity. Animals dosed with 100 times dietary requirement showed no evidence of toxicity (Goyer 1991). In humans, acute poisoning from foods or beverages prepared in galvanized containers is characterized by GI upset (Elinder 1986). Chronic oral toxicity in animals is associated with poor growth, GI inflammation, arthritis, lameness, and a microcytic, hypochromic anemia (Elinder 1986), possibly secondary to copper deficiency (Underwood 1977). The EPA (1997) presented a verified RfD of 0.3 mg/kg/day for chronic oral exposure to zinc, based on anemia in humans.

F.7.13.3 Carcinogenicity

The EPA (2000) classifies zinc in cancer weight-of-evidence Group D (not classifiable as to carcinogenicity to humans) based on inadequate evidence for carcinogenicity in humans and animals. The human data consist largely of occupational exposure studies not designed to detect a carcinogenic response, and of reports that prostatic zinc concentrations were lower in cancerous than in noncancerous tissue. The animal data consist of several dietary, drinking water, and zinc injection studies, none of which provided convincing data for a carcinogenic response.

F.7.14 Polyaromatic Hydrocarbons

PAHs are a large class of ubiquitous natural and anthropogenic chemicals, all with similar chemical structures (ATSDR 1990).

F.7.14.1 Pharmacokinetics

Although quantitative absorption data for the PAHs were not located, benzo(a)pyrene was readily absorbed across the GI (Rees et al. 1971) and respiratory epithelia (Kotin et al. 1969; Vainich et al. 1976). The high lipophilicity of other compounds in this class suggests that other PAHs also would be readily absorbed across GI and respiratory epithelia.

Benzo(a)pyrene was distributed widely in the tissues of treated rats and mice, but primarily to tissues high in fat, such as adipose tissue and mammary gland (Kotin et al. 1969; Schlede et al. 1970a). Patterns of tissue distribution of other PAHs would be expected to be similar because of the high lipophilicity of the members of this class.

Studies of the metabolism of benzo(a)pyrene provide information relevant to other PAHs because of the structural similarities of all members of the class. Metabolism involves microsomal mixed function oxidase hydroxylation of one or more of the phenyl rings with the formation of phenols and dihydrodiols, probably via formation of arene oxide intermediates (EPA 1979a). The dihydrodiols may be further oxidized to diol epoxides, which, for certain members of the class, are known to be the ultimate carcinogens (LaVoie et al. 1982).

Conjugation with glutathione or glucuronic acid, and reduction to tetrahydrotetrols are important detoxification pathways. Metabolism of naphthalene resulted in the formation of 1,2-naphthoquinone, which induced cataract formation and retinal damage in rats and rabbits.

Excretion of benzo(a)pyrene or dibenzo(a,h)anthracene residues was reported to be rapid, although quantitative data were not located (EPA 1979b). Excretion occurred mainly via the feces, probably largely due to biliary secretion (Schlede et al. 1970a, 1970b). The EPA (1980) concluded that accumulation in the body tissues of PAHs from chronic low level exposure would be unlikely.

F.7.14.2 Noncancer Toxicity

Oral noncancer toxicity data are available for acenaphthene, anthracene, fluoranthene, fluorene, and naphthalene. Newborn infants, children, and adults exposed to naphthalene by ingestion, inhalation, or possibly by skin contact developed hemolytic anemia with associated jaundice and occasionally renal disease (EPA 1979c). In a 13-week gavage study in rats, treatment with 50 mg naphthalene/kg, 5 days/week for 13 weeks (35.7 mg/kg/day) induced no effects; higher doses presumably reduced the growth rate (National Toxicology Program (NTP) 1980). Application of an uncertainty factor of 1000 yielded a provisional RfD for chronic oral exposure of 0.04 mg/kg/day (EPA 1997). The very mild effect (decreased growth rate) apparently observed at higher doses suggests that the RfD is very conservatively protective.

F.7.14.3 Carcinogenicity

The PAHs are ubiquitous, being released to the environment from anthropogenic as well as from natural sources (ATSDR 1992a). Benzo(a)pyrene is the most extensively studied member of the class, inducing tumors in multiple tissues of virtually all laboratory species tested by all routes of exposure. Although epidemiology studies suggested that complex mixtures that contain PAHs (coal tar, soots, coke oven emissions, cigarette smoke) are carcinogenic to humans (EPA 1984), the carcinogenicity cannot be attributed to PAHs alone because of the presence of other potentially carcinogenic substances in these mixtures (ATSDR 1992a). In addition, recent investigations showed that the PAH fraction of roofing tar, cigarette smoke, and coke oven emissions accounted for only 0.1 to 8 percent of the total

mutagenic activity of the unfractionated complex mixture in Salmonella (Lewtas 1988). Aromatic amines, nitrogen heterocyclic compounds, highly oxygenated quinones, diones, and nitrooxygenated compounds, none of which would be expected to arise from in vivo metabolism of PAHs, probably accounted for the majority of the mutagenicity of coke oven emissions and cigarette smoke. Furthermore, coal tar, which contains a mixture of many PAHs, has a long history of use in the clinical treatment of a variety of skin disorders in humans (ATSDR 1990).

Because of the lack of human cancer data, assignment of individual PAHs to EPA cancer weight-of-evidence groups was based largely on the results of animal studies with large doses of purified compound (EPA 1984). Frequently, unnatural routes of exposure, including implants of the test chemical in beeswax and trioctanoin in the lungs of female Osborne-Mendel rats, intratracheal instillation, and subcutaneous or intraperitoneal injection, were used. Benzo(a)anthracene, benzo(a)pyrene, dibenz(a,h)anthracene, and indeno(1,2,3-cd)pyrene were classified in Group B2 (probable human carcinogens).

The EPA (2000) verifies a slope factor for oral exposure to benzo(a)pyrene of 7.3 per mg/kg/day, based on several dietary studies in mice and rats. Neither verified nor provisional quantitative risk estimates were available for the other PAHs in Group B2. The EPA (1980) promulgated an ambient water quality criterion for "total carcinogenic PAHs," based on an oral slope factor derived from a study with benzo(a)pyrene, as being sufficiently protective for the class. Largely because of this precedent, the quantitative risk estimates for benzo(a)pyrene were adopted for the other carcinogenic PAHs when quantitative estimates were needed.

Recent reevaluations of the carcinogenity and mutagenicity of the Group B2 PAHs suggest that there are large differences between individual PAHs in cancer potency (Krewski et al., 1989). Based on the available cancer and mutagenicity data, and assuming that there is a constant relative potency between different carcinogens across different bioassay systems and that the PAHs under consideration have similar dose-response curves, Thorslund and Charnley (1988) derived relative potency values for several PAHs. A more recent Relative Potency Factor (RPF) scheme for the Group B2 PAHs was based only on the induction of lung epidermoid carcinomas in female Osborne-Mendel rats in the lung-implantation experiments (Clement International 1990).

F.7.15 Benzo[A]Anthracene

F.7.15.1 Noncancer Toxicity

The oral and inhalation RfD and RfC are not available at this time (EPA 2000).

F.7.15.2 Carcinogenicity

Benzo[a]anthracene has a weight of evidence classification of B2, a probable human carcinogen. The classification was based on sufficient data from animal bioassays. Benzo[a]anthracene produced tumors in mice exposed by gavage; intraperitoneal, subcutaneous or intramuscular injection; and topical application. Benzo[a]anthracene produced mutations in bacteria and in mammalian cells, and transformed mammalian cells in culture.

Although there are no human data that specifically link exposure to benzo[a]anthracene to human cancers, benzo[a]anthracene is a component of mixtures that have been associated with human cancer. These include coal tar, soot, coke oven emissions and cigarette smoke (U.S. EPA, 1984, 1990; IARC, 1984; Lee et al., 1976; Brockhaus and Tomingas, 1976).

Benzo[a]anthracene administration caused an increase in the incidence of tumors by gavage (Klein, 1963); dermal application (IARC, 1973); and both subcutaneous injection (Steiner and Faulk, 1951; Steiner and Edgecomb, 1952) and intraperitoneal injection (Wislocki et al., 1986) assays. A group of male mice was exposed to gavage solutions containing 3% benzo[a]anthracene for 5 weeks. There was an increased incidence of pulmonary adenomas and hepatomas.

Supporting data for carcinogenicity include genetic mutations in five different strains of Salmonella typhimurium. Benzo[a]anthracene produced positive results in an assay for mutations in Drosophila melongaster (Fahmy and Fahmy, 1973).

The currently used Oral Slope Factor (CSF) for Benzo[a]anthracene is 7.3E-01 per (mg/kg)/day which is extrapolated from the CSF for Benzo[a]pyrene (BaP), i.e., 0.1 x 7.3 (BaP)

= 7.3E-01 per (mg/kg)/day (USEPA Region III Risk-Based Concentration Table, 10/1/99). The inhalation CSF is not available.

F.7.16 Benzo(B)Fluoranthene

F.7.16.1 Noncancer Toxicity

Little information is available on benzo(b)fluoranthene. However based on the similarities of chemical structures, most properties should be similar to benzo(a)pyrene.

F.7.16.2 Carcinogenicity

A Toxicity Equivalency Factor (TEF) has been developed (EPA, 1993) for benzo(b)fluoranthene which allows the estimation of an oral CSF of 0.73 mg/g/day. The EPA (2000) has classified benzo(b)fluoranthene in cancer weight-of-evidence Group B2 (Probable Human Carcinogen, sufficient evidence of carcinogenicity in animals with inadequate or lack of evidence in humans) based on lung tumors in mice.

F.7.17 Benzo[A]Pyrene (BAP)

F.7.17.1 Pharmacokinetics

Benzo(a)pyrene was readily absorbed across the GI (Rees et al. 1971) and respiratory epithelia (Kotin et al. 1969; Vainich et al. 1976). Benzo(a)pyrene was distributed widely in the tissues of treated rats and mice, but primarily to tissues high in fat, such as adipose tissue and mammary gland (Kotin et al. 1969; Schlede et al. 1970a).

Studies of the metabolism of benzo(a)pyrene provide information relevant to other PAHs because of the structural similarities of all members of the class. Metabolism involves microsomal mixed function oxidase hydroxylation of one or more of the phenyl rings with the formation of phenols and dihydrodiols, probably via formation of arene oxide intermediates (EPA 1979a). The dihydrodiols may be further oxidized to diol epoxides, which, for certain members of the class, are known to be the ultimate carcinogens (LaVoie et al. 1982).

Conjugation with glutathione or glucuronic acid, and reduction to tetrahydrotetrols are important detoxification pathways.

Excretion of benzo(a)pyrene residue was reported to be rapid, although quantitative data were not located (EPA 1979b). Excretion occurred mainly via the feces, probably largely due to biliary secretion (Schlede et al. 1970a, 1970b). The EPA (1980) concluded that accumulation in the body tissues of PAHs from chronic low level exposure would be unlikely.

F.7.17.2 Noncancer Toxicity

The oral RfD and inhalation RfC are not available at this time.

F.7.17.3 Carcinogenicity

The PAHs are ubiquitous, being released to the environment from anthropogenic as well as from natural sources (ATSDR 1992a). Benzo (a)pyrene is the most extensively studied member of the class, inducing tumors in multiple tissues of virtually all laboratory species tested by all routes of exposure. Although epidemiology studies suggested that complex mixtures that contain PAHs (coal tar, soots, coke oven emissions, cigarette smoke) are carcinogenic to humans (EPA 1984), the carcinogenicity cannot be attributed to PAHs alone because of the presence of other potentially carcinogenic substances in these mixtures (ATSDR 1990). In addition, recent investigations showed that the PAH fraction of roofing tar, cigarette smoke, and coke oven emissions accounted for only 0.1 to 8 percent of the total mutagenic activity of the unfractionated complex mixture in Salmonella (Lewtas 1988). Aromatic amines, nitrogen heterocyclic compounds, highly oxygenated quinones, diones, and nitrooxygenated compounds, none of which would be expected to arise from in vivo metabolism of PAHs, probably accounted for the majority of the mutagenicity of coke oven emissions and cigarette smoke. Coal tar, which contains a mixture of many PAHs, has a long history of use in the clinical treatment of a variety of skin disorders in humans (ATSDR 1990).

Because of the lack of human cancer data, assignment of individual PAHs to EPA cancer weight-of-evidence groups was based largely on the results of animal studies with large doses of purified compound (EPA 1984). Frequently, unnatural routes of exposure, including implants of the test chemical in beeswax and trioctanoin in the lungs of female Osborne-Mendel rats,

intratracheal instillation, and subcutaneous or intraperitoneal injection, were used. Benzo (a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, chrysene, dibenzo(a,h)anthracene, and indeno(1,2,3-cd)pyrene were classified in Group B2 (probable human carcinogens).

The EPA (2000) verifies a slope factor for oral exposure to benzo(a)pyrene of 7.3 per mg/kg/day, based on several dietary studies in mice and rats. Neither verified nor provisional quantitative risk estimates were available for the other PAHs in Group B2. The EPA (1980) promulgated an ambient water quality criterion for "total carcinogenic PAHs," based on an oral slope factor derived from a study with benzo(a)pyrene, as being sufficiently protective for the class. Largely because of this precedent, the quantitative risk estimates for benzo(a)pyrene were adopted for the other carcinogenic PAHs when quantitative estimates were needed.

Human data specifically linking benzo[a]pyrene (BAP) to a carcinogenic effect are lacking. There are, however, multiple animal studies in many species demonstrating BAP to be carcinogenic following administration by numerous routes. In addition, BAP has produced positive results in numerous genotoxicity assays.

The data for animal carcinogenicity was sufficient. The animal data consist of dietary, gavage, inhalation, intratracheal instillation, dermal and subcutaneous studies in numerous strains of at least four species of rodents and several primates. Repeated BAP administration has been associated with increased incidences of total tumors and of tumors at the site of exposure. The tumor types in mice from oral diet studies include forestomach, squamous cell papillomas and carcinomas (Neal and Rigdon 1967).

Benzo [a]pyrene has been shown to cause genotoxic effects in a broad range of prokaryotic and mammalian cell assay systems (EPA 1990).

The oral slope factor presented in the Region III Risk-Based Concentration Table is 7.3E+0 per mg/kg/day. The cancer slope factor for inhalation is not available.

F.7.18 Dibenzo[A,H]Anthracene

F.7.18.1 Noncancer Toxicity

The oral RfD and inhalation RfC are not available.

F.7.18.2 Carcinogenicity

Classification -- B2; probable human carcinogen

The EPA (1997) has classified dibenzo(a,h)anthracene in cancer weight-of-evidence group B2 (Probable Human Carcinogen, sufficient evidence of carcinogenicity in animals). Based on carcinomas in mice following oral or dermal exposure and injection site tumors in several species following subcutaneous or intramuscular administration. Dibenzo[a,h]anthracene has induced DNA damage and gene mutations in bacteria as well as gene mutations and transformation in several types of mammalian cell cultures.

Although there are no human data that specifically link exposure to dibenzo[a,h]anthracene with human cancers, dibenzo[a]anthracene is a component of mixtures that have been associated with human cancer. These include coal tar, soot, coke oven emissions and cigarette smoke (EPA, 1984, 1990; IARC, 1984).

Dibenzo[a,h]anthracene has been shown to be carcinogenic when administered to mice by the oral route (Snell and Stewart, 1962, 1963) in a water-olive oil emulsion. Mice developed pulmonary adenomas, pulmonary carcinomas, and mammary carcinomas.

Dibenzo[a,h]anthracene has produced positive results in bacterial DNA damage and mutagenicity assays and in mammalian cell DNA damage, mutagenicity and cell transformation assays.

The currently used Oral Slope Factor (CSF) for Dibenzo[a,h]anthracene is 7.3E+00 per (mg/kg)/day which is extrapolated from the CSF for Benzo[a]pyrene i.e., 1.0 x 7.3 (BaP) = 7.3 per (mg/kg)/day) (USEPA Region III Risk-Based Concentration Table, 10/1/99).

The inhalation Cancer Slope Factor for dibenzo(a,h)anthracene is not available.

F.7.19 Indeno(1,2,3-Cd)Pyrene

F.7.19.1 Noncancer Toxicity

Little information was found on the toxicity of indeno(1,2,3-cd)pyrene. Because of its structural similarity its properties should resemble benzo(a)pyrene.

F.7.19.2 Carcinogenicity

A Toxicity Equivalency Factor (TEF) has been developed for indeno(1,2,3-cd)pyrene (EPA 1993). This allows the estimation of an oral CSF of 0.73 mg/kg/day. The EPA (2000) has classified indeno(1,2,3-cd)pyrene in cancer weight-of-evidence Group B2 (Probable Human Carcinogen, sufficient evidence of carcinogenicity in animals with inadequate or lack of evidence in humans) based on tumors in mice following lung implants.

F.7.20 Aldrin/Dieldrin (Clement 1985)

F.7.20.1 Pharmacokinetics

Both aldrin and dieldrin are carcinogens, causing increases in a variety of tumors in rats at low but not at high doses and producing a higher incidence of liver tumors in mice. The reason for this reversed dose-response relationship is unclear. Neither appears to be mutagenic when tested in a number of systems. Aldrin and dieldrin are both toxic to the reproductive system and teratogenic. Reproductive effects include decreased fertility, increased fetal death, and effects on gestation; while teratogenic effects include cleft palate, webbed foot, and skeletal anomalies. Chronic effects attributed to aldrin and dieldrin include liver toxicity and central nervous system abnormalities. Both chemicals are acutely toxic; the oral LD_{50} is around 50 mg/kg, and the dermal LD_{50} is about 100 mg/kg.

F.7.20.1 Non-Carcinogenic Toxicity

Chronic feeding with aldrin induced evidence of degeneration of the liver in rats. (EPA 1997). The EPA (1997) presented a verified chronic oral RfD of 0.03 ug/kg/day based on a LOAEL for liver effects in rats and an uncertainty factor of 1000. The principal target organ of aldrin is the liver.

F.7.20.2 Carcinogenicity

The EPA (1997) classifies aldrin in cancer weight-of-evidence Group B2 (probable human carcinogen), based on inadequate human data and sufficient animal data. The human data consist of epidemiologic studies that had results that were statistically insignificant. Animal studies associated treatment with liver tumors in male and female mice. The EPA (1997) presented a verified oral slope factor of 17 per mg/kg/day, based on the increased incidence of liver tumors in mice treated in the diet. An inhalation risk estimate was not derived.

F.7.21 Chlordane

Technical chlordane is a mixture of at least 50 related compounds (ATSDR 1992b). The principal components of the mixture are cis- and trans-chlordane, heptachlor, cis- and trans-nonachlor, and alpha-, beta- and gamma-chlordane. Each component has its own environmental fate and transport kinetics, so it is unlikely that the chlordane identified at the site would have the same chemical composition as technical chlordane. It is unclear which chlordane component(s) were found at the site.

F.7.21.1 Pharmacokinetics

Kinetic studies in rats, in which the area under the curve was compared following intravenous and oral dosing, indicate that approximately 80 percent of an oral dose of trans-chlordane is absorbed from the GI tract (Ohno et al. 1986). In animals, absorbed chlordane is distributed most rapidly to the liver and kidneys, probably because of the extensive vascularity of these organs (Ohno et al. 1986), followed by redistribution to adipose tissue (Barnett and Dorough 1974). In humans, levels of chlordane residues in adipose tissue increase with increasing

duration of exposure (ATSDR 1992b). Metabolism involves principally oxidation, dechlorination, and conjugation, yielding lipophilic products that accumulate in adipose tissue, as well as more polar products that are excreted. Chlordane residues are excreted principally through the bile, although considerable species differences occur. Lactation is an important mechanism of excretion of chlordane residues retained in body fat.

F.7.21.2 Non-Carcinogenic Toxicity

An acute oral lethal dose of chlordane in humans is estimated to be 25 to 50 mg/kg (ATSDR 1992b). Symptoms of acute oral or inhalation intoxication in humans consistently include GI disturbances such as vomiting, cramps, and diarrhea, and neurological effects including headache, irritability, dizziness, incoordination, convulsions, and coma. Data were not located regarding symptoms or effects in humans chronically exposed by the oral route, and no noncancer effects were observed in several studies of occupationally exposed humans. Mild liver lesions were observed in chronic oral studies in rats and mice. Prenatal or early postnatal exposure of mice to chlordane damages the developing immune system and nervous system. Target organs of chlordane include the liver, nervous system, and the fetus and neonate.

The EPA (1997) derived an RfD of 0.06 mg/kg/day for chronic oral exposure to chlordane, based on an NOEL of 0.055 mg/kg/day for liver effects in a 30-month dietary study in rats (Velsicol Chemical Company 1983). An uncertainty factor of 1,000 was applied; factors of 10 each for inter- and intraspecies variation, and to reflect deficiencies in the database.

F.7.21.3 Carcinogenicity

The EPA (2000) classifies chlordane in cancer weight-of-evidence Group B2, based on inadequate evidence in humans and sufficient evidence in animals. The human data consist of several epidemiologic studies of chlordane manufacturing workers and pesticide applicators. The only indication of a carcinogenic effect was a borderline significantly increased incidence of bladder cancer in one study of pesticide applicators, but chlordane exposure was not quantified and the workers were concomitantly exposed to other carcinogenic pesticides. The animal data consist of several studies in which oral exposure induced a dose-related increase in the incidence of liver tumors. The evidence for carcinogenicity in rats is equivocal. The

EPA (1997) derived an oral slope factor of 1.3 per mg/kg/day and an inhalation unit risk of 0.00037 per ug/m^3 based on liver tumor incidence in two dietary studies in mice. The unit risk is equivalent to an inhalation reference dose of 1.29 per mg/kg/day (EPA 1997), assuming humans inhale 20m^3 of air/day and weigh 70 kg.

F.7.22 Dieldrin

F.7.22.1 Noncancer Toxicity

The EPA (2000) derived a RfD of 5 x 10^{-5} mg/kg/day for chronic oral exposure based on a NOAEL of 0.005 mg/kg/day for liver lesions in a two-year rat feeding study (Walker et al., 1969) with an uncertainty factor of 100. The LOAEL was identified as 0.05 mg/kg/day.

At the end of two years the rats had increased liver weights and histopathological examinations revealed liver parenchymal cell changes. These hepatic lesions were considered to be characteristic of exposure to an organochlorine insecticide.

The chronic inhalation RfC is not available at this time.

F.7.22.2 Carcinogenicity

EPA (2000) classifies dieldrin in cancer weight-of-evidence B2. Dieldrin is carcinogenic in seven strains of mice when administered orally. Dieldrin is structurally related to compounds (aldrin, chlordane, heptachlor, heptachlor epoxide, and chlorendic acid) which produce tumors in rodents.

Human carcinogenicity data is considered inadequate. Two studies of workers exposed to aldrin and to dieldrin reported no increased incidence of cancer. Both studies were limited in their ability to detect an excess of cancer deaths.

Animal carcinogenicity data was sufficient. Dieldrin has been shown to be carcinogenic in various strains of mice of both sexes. At different dose levels the effects range from benign liver tumors, to hepatocarcinomas with transplantation confirmation, to pulmonary metastases.

Supporting data for carcinogenicty include genotoxicity tests. Dieldrin causes chromosomal aberrations in mouse cells (Markaryan, 1966; Majumdar et al., 1976) and in human lymphoblastoid cells (Trepanier et al., 1977), mutation in Chinese hamster cells (Ahmed et al., 1977), and unscheduled DNA synthesis in rat (Probst et al., 1981) and human cells (Rocchi et al., 1980).

EPA (2000) reports an Oral Slope Factor of 16 per (mg/kg)/day based on a diet study in mice that produced liver carcinomas.

This inhalation cancer slope factor of 16 per mg/kg/day was calculated from the oral slope factor.

F.7.23 Heptachlor Epoxide (Clement, 1985)

F.7.23.1 Health Effects

Heptachlor epoxide is a liver carcinogen when administered orally to mice. Results from mutagenicity bioassays suggest that this compound also may have genotoxic activity. Reproductive and teratogenic effects in rats include decreased litter size, shortened life span of suckling rats, and development of cataracts in offspring.

Tests with laboratory animals, primarily rodents, demonstrate acute and chronic toxic effects due to heptachlor exposure. Although heptachlor epoxide is absorbed most readily through the gastrointestinal tract, inhalation and skin contact are also potential routes of exposure. Acute exposure by various routes can cause development of hepatic vein thrombi and can effect the central nervous system and cause death. Chronic exposure induces liver changes, affects hepatic microsomal enzyme activity, and causes increased mortality in offspring. The oral LD_{50} for heptachlor epoxide in the rat is 47 mg/kg.

Although there are reports of acute and chronic toxicity in humans, with symptoms including tremors, convulsions, kidney damage, respiratory collapse, and death, details of such episodes are not well documented. Heptachlor epoxide has been found in a high percentage of human adipose tissue samples, and also in human milk samples and biomagnification of heptachlor

epoxide occurs. This compound also has been found in the tissues of stillborn infants, suggesting an ability to cross the placenta and bioaccumulate in the fetus.

The oral RfD for heptachlor epoxide is 1.30E-05 mg/kg-day based on increased liver to weight ratios in male and female dogs. Heptachlor epoxide is classified as a B2 carcinogen oral CSF for heptachlor epoxide is 9.1 per mg/kg-day based on an increased incidence of liver carcinomas. The inhalation CSF for heptachlor epoxide is 9.1 per mg/kg-day.

F.7.24 Polychlorinated Biphenyls

F.7.24.1 Noncancer Toxicity

Epidemiologic studies of women in the United States associated oral PCB exposure with low birth weight or retarded musculoskeletal or neurobehavioral development of their infants (ATSDR 1992d). Oral studies in animals established the liver as the target organ in all species, and the thyroid as an additional target organ in the rat. Effects observed in monkeys included gastritis, anemia, chloracne-like dermatitis, and immunosuppression. Oral treatment of animals induced developmental effects, including retarded neurobehavioral and learning development in monkeys. Oral RfD values of 0.02 ug/kg/day for Aroclor-1254 and 0.07 ug/kg/day for Aroclor-1016 were located.

Occupational exposure to PCBs was associated with upper respiratory tract and ocular irritation, loss of appetite, liver enlargement, increased serum concentrations of liver enzymes, skin irritation, rashes and chloracne, and, in heavily exposed female workers, decreased birth weight of their infants (ATSDR 1992d). Concurrent exposure to other chemicals confounded the interpretation of the occupational exposure studies. Laboratory animals exposed by inhalation to Aroclor-1254 vapors exhibited moderate liver degeneration, decreased body weight gain and slight renal tubular degeneration. Neither subchronic nor chronic inhalation RfC values were available.

Target organs for PCBs include the skin, liver, fetus, and neonate.

F.7.24.2 Carcinogenicity

The EPA (2000) classifies the PCBs as EPA cancer weight-of-evidence Group B2 substances (probable human carcinogens), based on inadequate data in humans and sufficient data in animals. The human data consist of several epidemiologic occupational and accidental oral exposure studies with serious limitations, including poorly quantified concentrations of PCBs and durations of exposure, and probable exposures to other potential carcinogens.

The animal data consist of several oral studies in rats and mice with various aroclors, kanechlors, or clophens (commercial PCB mixtures manufactured in the United States, Japan and Germany, respectively) that reported increased incidence of liver tumors in both species (EPA 2000).

The EPA (2000) presents a verified oral slope factor and an inhalation slope factor of 2.0 per mg/kg/day for PCBs based on liver tumors in rats treated with Aroclor-1260.

F.7.25 Dioxins

Specific congeners and homologues of these classes of interest at this site include 1,2,3,4,6,7,8-heptachlorodibenzofuran and -heptachlorodibenzo-p-dioxin; 1,2,3,4,7,8,9-heptachlorodibenzofuran and -heptachlorodibenzo-p-dioxin; 1,2,3,4,7,8-hexachloro-dibenzofuran and -hexachlorodibenzo-p-dioxin; 1,2,3,6,7,8- and 2,3,4,6,7,8-hexachloro-dibenzofuran; 1,2,3,7,8,9-hexachlorodibenzofuran and -hexachlorodibenzo-p-dioxin; 1,2,3,6,7,8-hexachlorodibenzo-p-dioxin; unspecified hexachlorodibenzofurans and dibenzo-p-dioxins; 1,2,3,7,8- and 2,3,4,7,8-pentachlorodibenzofuran; unspecified pentachlorodibenzo-furans; 2,3,7,8-tetrachlorodibenzofuran; and unspecified tetrachloro-dibenzofurans.

F.7.25.1 Noncancer Toxicity

Of the members of these classes, the toxicity of 2,3,7,8-TCDD has been studied most extensively. The only effect in humans clearly attributable to 2,3,7,8-TCDD was chloracne (ATSDR 1999). The data, however, also associated exposure to 2,3,7,8-TCDD with hepatotoxicity and neurotoxicity in humans. In animals, toxicity of 2,3,7,8-TCDD is most

commonly manifested as a wasting syndrome with thymic atrophy, terminating in death, with a large number of organ systems showing nonspecific effects. Chronic treatment of animals with 2,3,7,8-TCDD or a mixture of two isomers of hexachlorodibenzo-p-dioxin resulted in liver damage. Immunologic effects may be among the more sensitive endpoints of exposure to the PCDDs in animals. In animals 2,3,7,8-TCDD is a developmental and reproductive toxicant. No verified or provisional noncancer toxicity values were located for any of the chemicals of interest in these classes (EPA 1999, 2000).

F.7.25.3 Carcinogenicity

Data regarding the carcinogenicity of 2,3,7,8-TCDD to humans, obtained from epidemiologic studies of workers exposed to pesticides or to other chlorinated chemicals known to be contaminated with 2,3,7,8-TCDD, are conflicting (ATSDR 1999). The interpretation of these studies is not clear because exposure to 2,3,7,8-TCDD was not quantified, multiple routes of exposure (dermal, inhalation, oral) were involved, and the workers were exposed to other potentially carcinogenic compounds. In animals, however, 2,3,7,8-TCDD is clearly carcinogenic, inducing thyroid, lung, and liver tumors in orally treated rats and mice (EPA 1985). Similarly, oral treatment with a mixture of two hexachlorodibenzo-p-dioxin isomers induced liver tumors in rats and mice. On the basis of the animal data, 2,3,7,8-TCDD and the hexachlorodibenzo-p-dioxins were assigned to EPA cancer weight-of-evidence Group B2 (probable human carcinogen). Although the other PCDDs and PCDFs were not formally classified as to carcinogenicity to humans, for regulatory purposes they are treated as probable human carcinogens.

The EPA (1997) presents provisional oral and inhalation slope factors for 2,3,7,8-TCDD of 150,000 per mg/kg/day, based on the incidence of liver and lung tumors in an oral study in rats.

Much less is known about the toxicity of other cdd and cdf congeners. Based on available toxicity data, epa has developed a method for expressing toxicities of these compounds in terms of equivalent amounts of 2,3,7,8-tcdd. "Toxicity equivalency factors", or tefs, are used to convert the concentration of a given cdd/cdf into an equivalent concentration of 2,3,7,8-tcdd.

F.7.26 Asbestos

F.7.26.1 Noncancer Toxicity

Data not available at this time.

F.7.26.2 Carcinogenicity

This section provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to the following sections for information on long-term toxic effects other than carcinogenicity.

Weight-Of-Evidence Classification

Classification -- A; human carcinogen

Basis -- Observation of increased mortality and incidence of lung cancer, mesotheliomas and gastrointestinal cancer in occupationally exposed workers are consistent across investigators and study populations. Animal studies by inhalation in two strains of rats showed similar findings for lung cancer and mesotheliomas. Animal evidence for carcinogenicity via ingestion is limited (male rats fed intermediate-range chrysotile fibers; i.e., >10 um length, developed benign polyps), and epidemiologic data in this regard are inadequate.

Human Carcinogenicity Data

Sufficient. Numerous epidemiologic studies have reported an increased incidence of deaths due to cancer, primarily lung cancer and mesotheliomas associated with exposure to inhaled asbestos. Among 170 asbestos insulation workers in North Ireland followed for up to 26 years, an increased incidence of death was seen due to all cancers (SMR=390), cancers of the lower respiratory tract and pleura (SMR=1760) (Elmes and Simpson, 1971) and mesothelioma (7 cases). Exposure was not quantified.

Selikoff (1976) reported 59 cases of lung cancer and 31 cases of mesothelioma among 1249 asbestos insulation workers followed prospectively for 11 years. Exposure was not quantified. A retrospective cohort mortality study (Selikoff et al., 1979) of 17,800 U.S. and Canadian asbestos insulation workers for a 10-year period using best available information (autopsy, surgical, clinical) reported an increased incidence of cancer at all sites (319.7 expected vs. 995 observed, SMR=311) and cancer of the lung (105.6 expected vs. 486 observed, SMR=460). A modest increase in deaths from gastrointestinal cancer was reported along with 175 deaths from mesothelioma (none expected). Years of exposure ranged from less than 10 to greater than or equal to 45. Levels of exposure were not quantified. In other pidemiologic studies, the increase for lung and pleural cancers has ranged from a low of 1.9 times the expected rate, in asbestos factory workers in England (Peto et al., 1977), to a high of 28 times the expected rate, in female asbestos textile workers in England (Newhouse et al., 1972). Other occupational studies have demonstrated asbestos exposure-related increases in lung cancer and mesothelioma in several industries including textile manufacturing, friction products manufacture, asbestos cement products, and in the mining and milling of asbestos. The studies used for the inhalation quantitative estimate of risk are listed in the table in Section II.C.2.

A case-control study (Newhouse and Thompson, 1965) of 83 patients with mesothelioma reported 52.6% had occupational exposure to asbestos or lived with asbestos workers compared with 11.8% of the controls. Of the remaining subjects, 30.6% of the mesothelioma cases lived within one-half mile of an asbestos factory compared with 7.6% of the controls.

The occurrence of pleural mesothelioma has been associated with the presence of asbestos fibers in water, fields and streets in a region of Turkey with very high environmental levels of naturally-occurring asbestos (Baris et al., 1979).

Kanarek et al. (1980) conducted an ecologic study of cancer deaths in 722 census tracts in the San Francisco Bay area, using cancer incidence data from the period of 1969-1971. Chrysotile asbestos concentrations in drinking water ranged from nondetectable to 3.6E+7 fibers/L. Statistically significant dose-related trends were reported for lung and peritoneal cancer in white males and for gall bladder, pancreatic and peritoneal cancer in white females. Weaker correlations were reported between asbestos levels and female esophageal, pleural and kidney cancer, and stomach cancer in both sexes. In an extension of this study, Conforti et al. (1981) included cancer incidence data from the period of 1969-1974. Statistically significant positive associations were found between asbestos concentration and cancer of the digestive organs in white females, cancers of the digestive tract in white males and esophageal, pancreatic and stomach cancer in both sexes. These associations appeared to be independent of socioeconomic status and occupational exposure to asbestos.

Marsh (1983) reviewed eight independent ecologic studies of asbestos in drinking water carried out in five geographic areas. It was concluded that even though one or more studies found an association between asbestos in water and cancer mortality (or incidence) due to neoplasms of various organs, no individual study or aggregation of studies exists that would establish risk levels from ingested asbestos. Factors confounding the results of these studies include the possible underestimates of occupational exposure to asbestos and the possible misclassification of peritioneal mesothelioma as GI cancer.

Polissar et al. (1984) carried out a case-control study which included better control for confounding variables at the individual level. The authors concluded that there was no convincing evidence for increased cancer risk from asbestos ingestion. At the present time, an important limitation of both the case-control and the ecologic studies is the short follow-up time relative to the long latent period for the appearance of tumors from asbestos exposure.

Animal Carcinogenicity Data

Sufficient. There have been about 20 animal bioassays of asbestos. Gross et al. (1967) exposed 61 white male rats (strain not reported) to 86 mg chrysotile asbestos dust/cu.m for 30 hours/week for 16 months. Of the 41 animals that survived the exposure period, 10 had lung cancer. No lung cancer was observed in 25 controls.

Reeves (1976) exposed 60-77 rats/group for 4 hours/day, 4 days/week for 2 years to doses of 48.7-50.2 mg/cu.m crocidolite, 48.2-48.6 mg/cu.m amosite and 47.4-47.9 mg/cu.m chrysotile. A 5-14% incidence of lung cancer was observed among concentration groups and was concentration-dependent.

Wagner et al. (1974) exposed CD Wistar rats (19-52/group) to 9.7-14.7 mg/cu.m of several types of asbestos for 1 day to 24 months for 7 hours/day, 5 days/week. A duration-dependent increased incidence of lung carcinomas and mesotheliomas was seen for all types of asbestos after 3 months of exposure compared with controls.

F344 rats (88-250/group) were exposed to intermediate range chrysotile asbestos (1291E+8 f/g) in drinking water by gavage to dams during lactation and then in diet throughout their lifetime (NTP, 1985). A statistically significant increase in incidence of benign epithelial neoplasms (adenomatous polyps in the large intestine) was observed in male rats compared with pooled controls of all NTP oral lifetime studies (3/524). In the same study, rats exposed to short range chrysotile asbestos (6081E+9 f/g) showed no significant increase in tumor incidence.

Ward et al. (1980) administered 10 mg UICC amosite asbestos 3 times/week for 10 weeks by gavage to 50 male F344 rats. The animals were observed for an additional 78-79 weeks post-treatment. A total of 17 colon carcinomas were observed. This result was statistically significant compared with historical controls; no concurrent controls were maintained.

Syrian golden hamsters (126-253/group) were exposed to short and intermediate range chrysotile asbestos at a concentration of 1% in the diet for the lifetime of the animals (NTP, 1983). An increased incidence of neoplasia of the adrenal cortex was observed in both males

and females exposed to intermediate range fibers and in males exposed to short range fibers. This increase was statistically significant by comparison to pooledcontrols but not by comparison to concurrent controls. NTP suggested that the biologic importance of adrenal tumors in the absence of target organ (GI tract) neoplasia was questionable.

Quantitative Estimate Of Carcinogenic Risk From Oral Exposure

Not available.

Quantitative Estimate Of Carcinogenic Risk From Inhalation Exposure

SUMMARY OF RISK ESTIMATES

Inhalation Unit Risk -- 2.3E-1 per (f/mL)

Extrapolation Method -- Additive risk of lung cancer and mesothelioma, using relative risk model for lung cancer and absolute risk model for mesothelioma.

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	4E-4 f/mL
E-5 (1 in 100,000)	4E-5 f/mL
E-6 (1 in 1,000,000)	4E-6 f/mL

Additional Comments (Carcinogenicity, Inhalation Exposure)

Risks have been calculated for males and females according to smoking habits for a variety of exposure scenarios (U.S. EPA, 1986). The unit risk value is calculated for the additive combined risk of lung cancer and mesothelioma, and is calculated as a composite value for males and females. The epidemiological data show that cigarette smoking and asbestos exposure interact synergistically for production of lung cancer and do not interact with regard

to mesothelioma. The unit risk value is based on risks calculated using U.S. general population cancer rates and mortality patterns without consideration of smoking habits. The risks associated with occupational exposure were adjusted to continuous exposure by applying a factor of 140 cu.m/50 cu.m based on the assumption of 20 cu.m/day for total ventilation and 10 cu.m/8-hour workday in the occupational setting.

The unit risk is based on fiber counts made by phase contrast microscopy (PCM) and should not be applied directly to measurements made by other analytical techniques. The unit risk uses PCM fibers because the measurements made in the occupational environment use this method. Many environmental monitoring measurements are reported in terms of fiber counts or mass as determined by transmission electron microscopy (TEM). PCM detects only fibers longer than 5 um and >0.4 um in diameter, while TEM can detect much smaller fibers. TEM mass units are derived from TEM fiber counts. The correlation between PCM fiber counts and TEM mass measurements is very poor. Six data sets which include both measurements show a conversion between TEM mass and PCM fiber count that range from 5-150 (ug/cu.m)/(f/mL). The geometric mean of these results, 30 (ug/cu.m)/(f/mL), was adopted as a conversion factor (U.S. EPA, 1986), but it should be realized that this value is highly uncertain. Likewise, the correlation between PCM fiber counts and TEM fiber counts is very uncertain and no generally applicable conversion factor exists for these two measurements.

In some cases TEM results are reported as numbers of fibers <5 um long and of fibers longer than 5 um. Comparison of PCM fiber counts and TEM counts of fibers >5 um show that the fraction of fibers detected by TEM that are also >0.4 um in diameter (and detectable by PCM) varies from 22-53% (U.S. EPA, 1986).

It should be understood that while TEM can be specific for asbestos, PCM is a nonspecific technique and will measure any fibrous material. Measurements by PCM which are made in conditions where other types of fibers may be present may not be reliable.

In addition to the studies cited above, there were three studies of asbestos workers in mining and milling which showed an increase in lung cancer (McDonald et al., 1980, Nicholson et al., 1979; Rubino et al., 1979). The slope factor calculated from these studies was lower than the other studies, possibly because of a substantially different fiber size distribution, and they were

not included in the calculation. The slope factor was calculated by life table methods for lung cancer using a relative risk model, and for mesothelioma using a absolute risk model. The final slope factor for lung cancer was calculated as the weighted geometric mean of estimates from the 11 studies cited in section II.C.2. The final slope factor for mesothelioma is based on the calculated values from the studies of Selikoff et al. (1979), Peto et al. (1982), Seidman et al. (1979), Peto (1980) and Finkelstein (1983) adjusted for the mesothelioma incidence from several additional studies cited previously.

There is some evidence which suggests that the different types of asbestos fibers vary in carcinogenic potency relative to one another and site specificity. It appears, for example, that the risk of mesothelioma is greater with exposure to crocidolite than with amosite or chrysotile exposure alone. This evidence is limited by the lack of information on fiber exposure by mineral type. Other data indicates that differences in fiber size distribution and other process differences may contribute at least as much to the observed variation in risk as does the fiber type itself.

The unit risk should not be used if the air concentration exceeds 4E-2 fibers/ml, since above this concentration the slope factor may differ from that stated.

Discussion Of Confidence (Carcinogenicity, Inhalation Exposure)

A large number of studies of occupationally-exposed workers have conclusively demonstrated the relationship between asbestos exposure and lung cancer or mesothelioma. These results have been corroborated by animal studies using adequate numbers of animals. The quantitative estimate is limited by uncertainty in the exposure estimates, which results from a lack of data on early exposure in the occupational studies and the uncertainty of conversions between various analytical measurements for asbestos.

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